

REMARKS

Claims 13-17 are all the claims pending in the application.

Proposed Amendments to the Claims

In drafting the Amendment filed July 10, 2003, Applicants inadvertently miss-abbreviated Hemagglutinating Virus of Japan (HVJ) as “HJV” in claims 13-17. Please see the present specification, pages 26-29, and Morishita et al. (U.S. Patent No. 6,248,722), column 5 line 23, for the correct abbreviation.

Accordingly, claims 13-17 have been amended to change “HJV” to “HVJ.” Entry of this amendment is respectfully requested.

Claim Rejections Under 35 U.S.C. § 103(a)

At page 2 of the Office Action, the Examiner maintained the rejection of claims 13-17 under 35 U.S.C. § 103(a), first set forth in the previous Office Action dated April 11 2003, as being unpatentable over Isner et al. (U.S. Patent No. 6,121,246 or WO 97/14307) (hereinafter “Isner”) and Morishita et al. (U.S. Patent No. 6,248,722) (hereinafter “Morishita”), in view of Ghodsi et al. (Human Gene Therapy 9:2331 (1998)) (hereinafter “Ghodsi”).

Amended claims 13-17 recite therapeutic or preventative methods for cerebrovascular disorders comprising introducing hepatocyte growth factor (HGF) and/or vascular endothelial growth factor (VEGF) genes in the form of HVJ-liposomes by direct injection into the subarachnoid space. On page 4 of the outstanding Office Action, the Examiner contended that Isner teaches local injection of HGF and VEGF genes for treatment of cerebrovascular ischemia.

The Examiner also stated that Morishita teaches expression of HGF via HVJ-liposomes, use of HGF to treat many different diseases including nervous disorders and arterial diseases, and *in vivo* administration directly into brain tissue. Finally, the Examiner relied on Ghodsi for demonstrating introduction of a genetic vector directly into the subarachnoid space.

Accordingly, the Examiner concluded on page 4 of the outstanding Office Action that it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the methods taught by Isner and Morishita by administering the HGF and/or VEGF genes in the form of HVJ-liposomes into the subarachnoid space with a reasonable expectation of success.

Applicants respectfully traverse this objection, and assert that based on the references cited above, one skilled in the art would not have predicted with reasonable certainty that HGF and/or VEGF genes administered in the form of HVJ-liposomes into the subarachnoid space would be effective for treatment of cerebrovascular disorders. Because of the unpredictability of gene therapy, and the unique characteristics of the central nervous system, a person skilled in the art at the time of the invention would not have expected HGF and/or VEGF genes injected into the subarachnoid space to be effectively expressed in the brain.

Isner and Morishita teach local injection of VEGF and HGF genes for treating ischemia. However, neither reference teaches injection into the subarachnoid space. At column 4, lines 2-7, Isner provides a list of diseases potentially treatable by the disclosed methods, and includes cerebrovascular ischemia. However, the specification describes only intramuscular gene transfer. See Example 1. Similarly, Morishita states that HGF genes may be administered

directly to diseased organs including the brain (see column 6, lines 5-11) but fails to demonstrate *in vivo* administration to any site other than cardiac muscle (see Test Example 8) and skeletal muscle (Test example 9). Thus, neither Isner nor Morishita enables gene transfer to the central nervous system. Further, although Ghodsi teaches the treatment of mucopolysaccharidosis by intracerebral injection of the β -glucuronidase gene, Ghodsi does not teach the treatment of cerebrovascular diseases, or the use of VEGF or HGF genes.

A skilled artisan would not have been motivated to combine the teachings of these references with a reasonable expectation of success in achieving the claimed invention, in part because gene therapy remains an unpredictable art. The poor efficiency of gene transfection using viral vectors in the central nervous system, in particular, has limited the development of gene therapy in the brain. See, e.g., Youichi Saitoh, et al., *Gene Therapy for Ischemic Brain Diseases*, Current Gene Therapy (2003), vol. 3, no. 1, pp. 49-58. Thus, successful intracerebral injection of the unrelated β -glucuronidase gene, combined with intramuscular VEGF and HGF gene transfer, would not have created a reasonable expectation that injection of VEGF and HGF genes into the subarachnoid space would result in significant levels VEGF and HGF protein expression in the brain.

Furthermore, the structure and the diseases of the central nervous system differ significantly from those of other organs. For example, the brain is more susceptible to ischemia than the heart and other organs. See, e.g. Youichi Saitoh, et al., *Gene Therapy for Ischemic Brain Diseases*, Current Gene Therapy (2003), vol. 3, no. 1, pp. 49-58. In addition, brain diseases are notoriously difficult to treat. Although cerebral hypoperfusion caused by cerebral

occlusive disorders is known to lead to cerebral ischemic events, a clinically effective treatment has not yet been established. See Shen-ichi Yoshimura, et al., *Gene Transfer of Hepatocyte Growth Factor to Subarachnoid Space in Cerebral Hypoperfusion Model*, Hypertension, May 2002, vol. 39, pp. 1028-1034.

Because of the fundamental differences between diseases of the brain and diseases of other organs, such as the skeletal and cardiac muscles disclosed in Isner and Morishita et al., success in inducing angiogenesis in ischemic heart and skeletal muscle, by intramuscular transfection of HGF and/or VEGF genes, would not have led a skilled artisan to reasonably expect that gene therapy would prove to be an effective treatment for cerebral occlusive diseases.

In conclusion, the present inventors have unexpectedly found that HGF and/or VEGF genes transferred into the subarachnoid space can improve cerebral hypoperfusion, and that the transfection of HGF genes into the subarachnoid space can prevent delayed neuronal death.

Applicants assert that it would not have been obvious to one of ordinary skill in the art at the time the invention was made to modify the methods taught by Isner and Morishita by administering the HGF and/or VEGF genes in the form of HVJ-liposomes into the subarachnoid space with a reasonable expectation of success.

In view of the foregoing, the claimed invention is not obvious over Isner and Morishita in view of Ghodsi. Accordingly, Applicants respectfully request withdrawal of the rejection. Reconsideration and allowance of this application are now believed to be in order, and such actions are hereby solicited. If any points remain in issue which the Examiner feels may be best

JAN 06 2004

Amendment Under 37 C.F.R. § 1.116
U.S. Appln. No.: 09/856,374

Attorney Docket No.: Q64360

resolved through a personal or telephone interview, the Examiner is kindly requested to contact the undersigned at the telephone number listed below.

The USPTO is directed and authorized to charge all required fees, except for the Issue Fee and the Publication Fee, to Deposit Account No. 19-4880. Please also credit any overpayments to said Deposit Account.

Respectfully submitted,

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23373
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Date: January 6, 2004